Séminaire FRANCOPA
Des nouvelles approches méthodologiques (NAM) pour les tests de toxicité réglementaires: actualités et perspectives

La place des méthodes alternatives dans les règlements révisés de CLP et de REACH : perspectives de la Commission

(Dr Sylvain Bintein, DG Env)

~ 100 000 chemicals
on the market

~ 22 600 chemicals
with a use over
1 tonne per year

~ 4 700 chemicals
with a use over
100 tonnes per year
prioritised in
hazard characterisation
and evaluation

https://www.eea.europa.eu/soer

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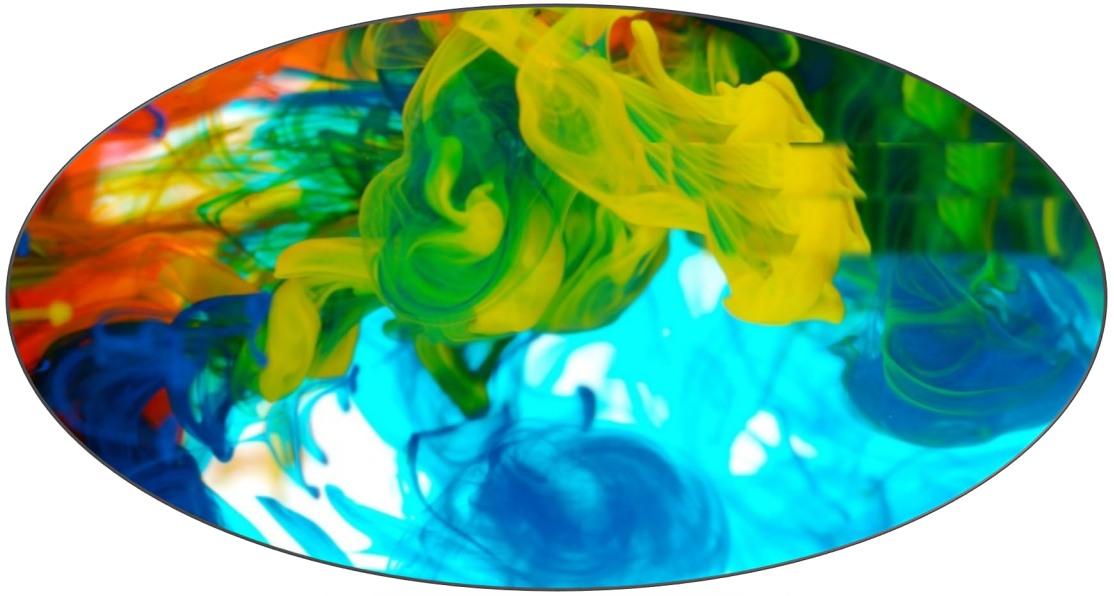
REACH Information Requirements

CSS Action led by JRC with support of steering group (DG ENV, DG GROW, ECHA)

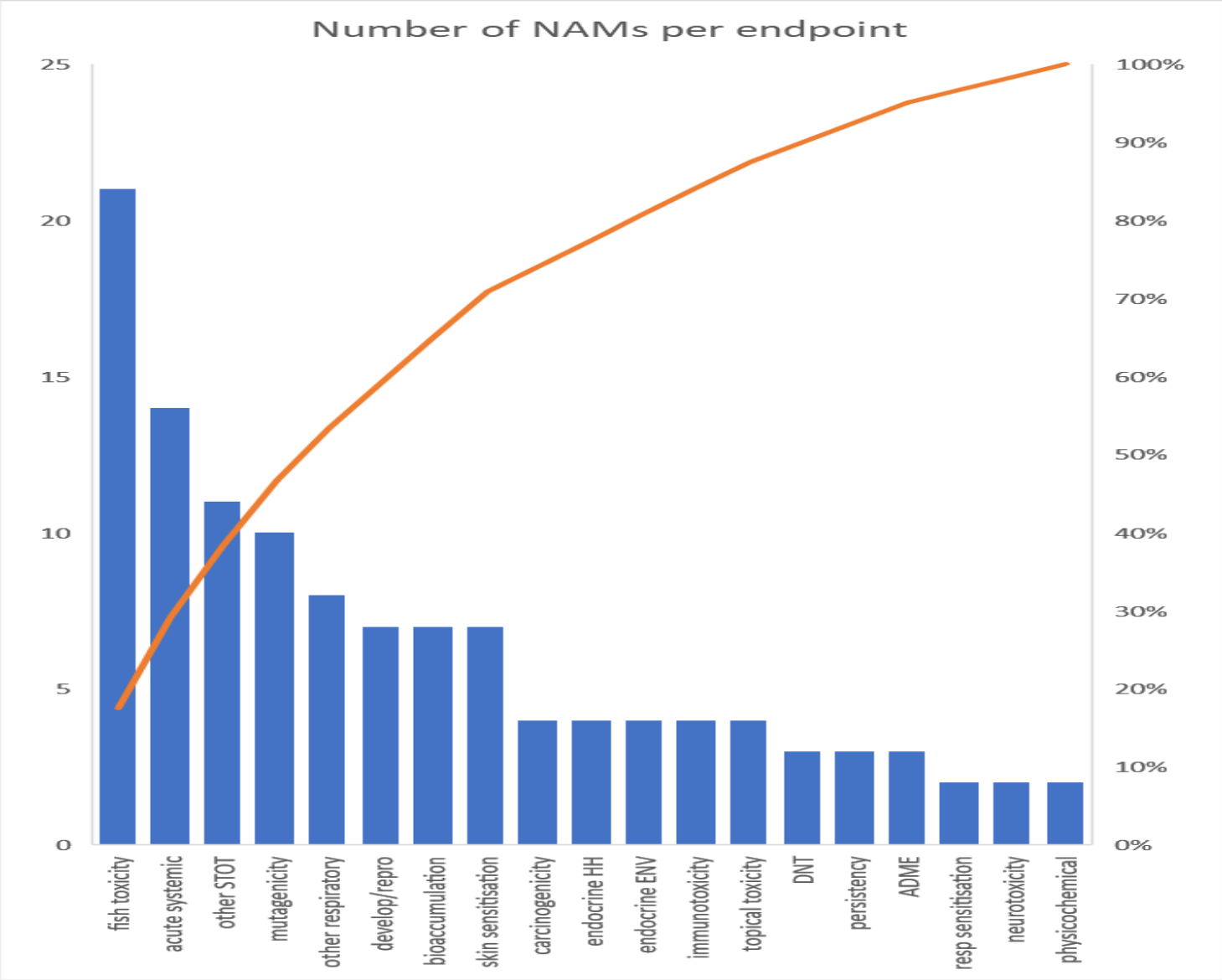


- **Enable Chemical Safety Assessment at Annex VII (DNELs & PNECs)**
- **Inclusion of critical hazards (at Annex VII)**

  carcinogenicity, mutagenicity, reproductive toxicity,
  endocrine disruption, neurotoxicity, respiratory sensitisation, immunotoxicity, and other specific target organ toxicity,
  persistent, bioaccumulative and toxic

- **Information on toxicokinetic properties & mode of action (supporting grouping, read-across, IVIVE)**

EU Survey responses as of 24-01-22: 78 responses



More methods:

- Skin sensitisation, skin irritation, eye irritation, physicochemical properties
- Aquatic toxicity (fish, daphnids, algae), bioaccumulation and persistency
- Genotoxicity
- Acute systemic toxicity
- Other STOT (liver, kidney, cardiotoxicity)
- Developmental / reproductive toxicity
- Respiratory irritation

Fewer methods:

- Carcinogenicity
- Immunotoxicity
- DNT
- Endocrine (HH and ENV)
- ADME
- Respiratory sensitisation

Background – NAMs in REACH

Non-animal new approach methodologies are standard requirements for local toxicity requirements

- Skin irritation / corrosion
- Eye irritation / corrosion
- Skin sensitisation
- Mutagenicity

Success!

NAM-based adaptations are possible in principle for systemic toxicity / more complex endpoints but rarely accepted because

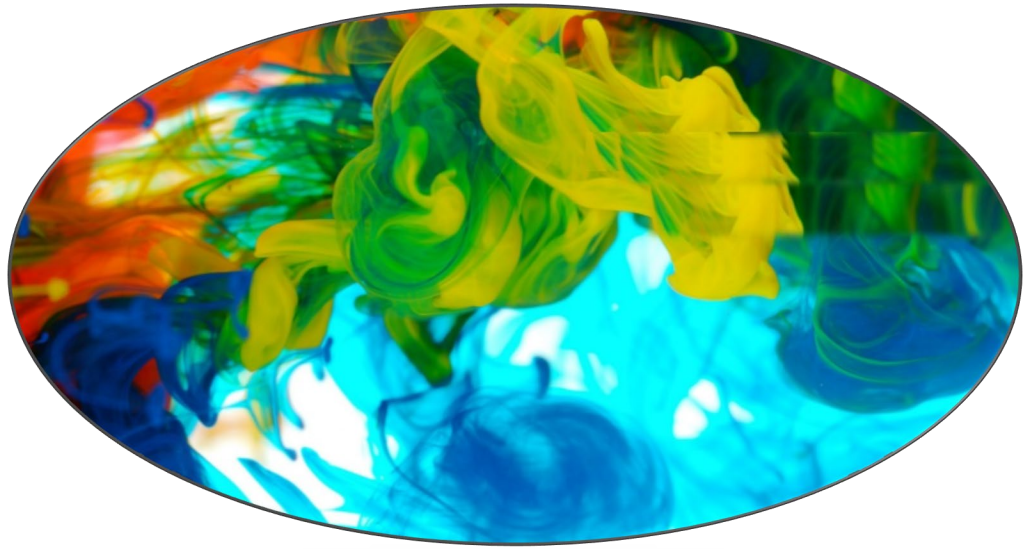
- Mechanistic understanding of systemic toxicity still incomplete

- NAMs cannot predict adversity as asked by current REACH

The Issue!

REACH Information Requirements

…only using NAMs available today? :



- **Enable Chemical Safety Assessment at all tonnage levels** *(28-day study)*

- **Inclusion of critical hazards**

  carcinogenicity, mutagenicity, reproductive toxicity, endocrine disruption, neurotoxicity, respiratory sensitisation, immunotoxicity, and other specific target organ toxicity, persistent, bioaccumulative and toxic

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NAM-based information requirements to be added in Annex VII:

- ADME / TK (minimal NAM battery):
  - High Throughput data on fraction unbound plasma, *in vitro* hepatic clearance and *in vitro* uptake* (many years of experience, robust and reliable methods available, possible to describe in guidance)
- Endocrine disruption (NAM battery for ER and AR)
- Bioaccumulation in aquatic species (minimal NAM battery)
  - Intrinsic clearance in rainbow trout hepatocytes (OECD TG 319A) or S9 fraction (OECD TG 319B)
- Acute fish toxicity (fish cell line; OECD TG 249)

* **OECD Guidance document on the characterisation, validation and reporting of Physiologically Based Kinetic (PBK) models for regulatory purposes**

Excluded from IA:

- respiratory sensitisation, (developmental) immunotoxicity and developmental neurotoxicity because no standardised NAMs or batteries ready for regulatory use yet.

Regulatory context – current system

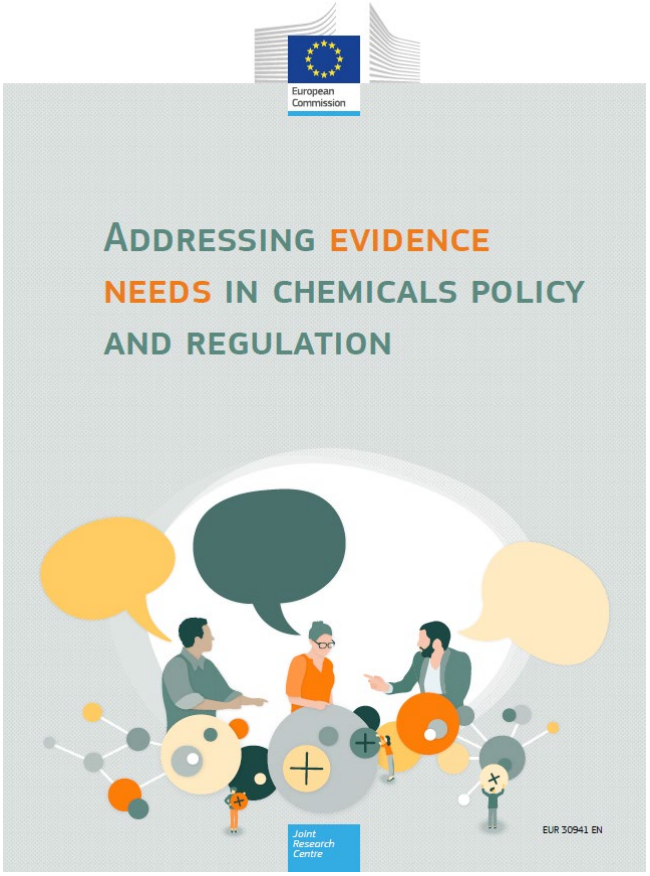
→ The regulatory system for industrial chemicals management relies on a **horizontal generic approach** based on the **identification of hazardous properties** of substances.

→ **CLP Regulation** is the cornerstone legislation which:

- Enables the **identification of hazardous properties and classification** based on adverse effects, **independently of exposure**, by applying specific criteria agreed at EU and international level (GHS),
- ensures, through **harmonised classification and labelling** that appropriate classification is consistently applied for most hazardous substances and can be easily enforced
- has **direct impact on other EU legislations**, including REACH, pesticide, biocide, cosmetic legislation, legislation regulating worker protection, etc.
- enables efficient **hazard communication** to workers, downstream users, consumers
- provides a **framework for generic risk management**.

Problems
with introducing New Approach Methods (NAMs) in regulation

- NAMs not standardised or validated enough? (OECD TG required?)
- NAMs for systemic toxicity – not there and no 1 to 1 replacement possible
- NAMS mainly allow conclusion for category 2 => problem with Generic Risk management approach (e.g., CMI in cosmetics)
- Perception of “less safe” & higher uncertainty
  - Competent authorities: level of acceptability higher when more protective
  - Industry (CEFIC) in favor of NAMS but what about specific Companies for their own substances =>level of acceptability higher for negative (non-CMR) compared to positive (CMR)
- Short/medium solution: grouping approach??
- Are there incentives for researchers to develop methods for regulatory use?
- Lack of trust between key players – how to create confidence together?



https://publications.jrc.ec.europa.eu/repository/handle/JRC126724

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Beyond this REACH revision – long term perspective

Where do we want to go?

- achieve higher safety by having a **basic knowledge about a higher number of substances** while requiring **less information for each substance**
- minimise animal testing with **eventual aim of complete replacement**

Suggest to develop a roadmap

Roadmap for chemicals legislation

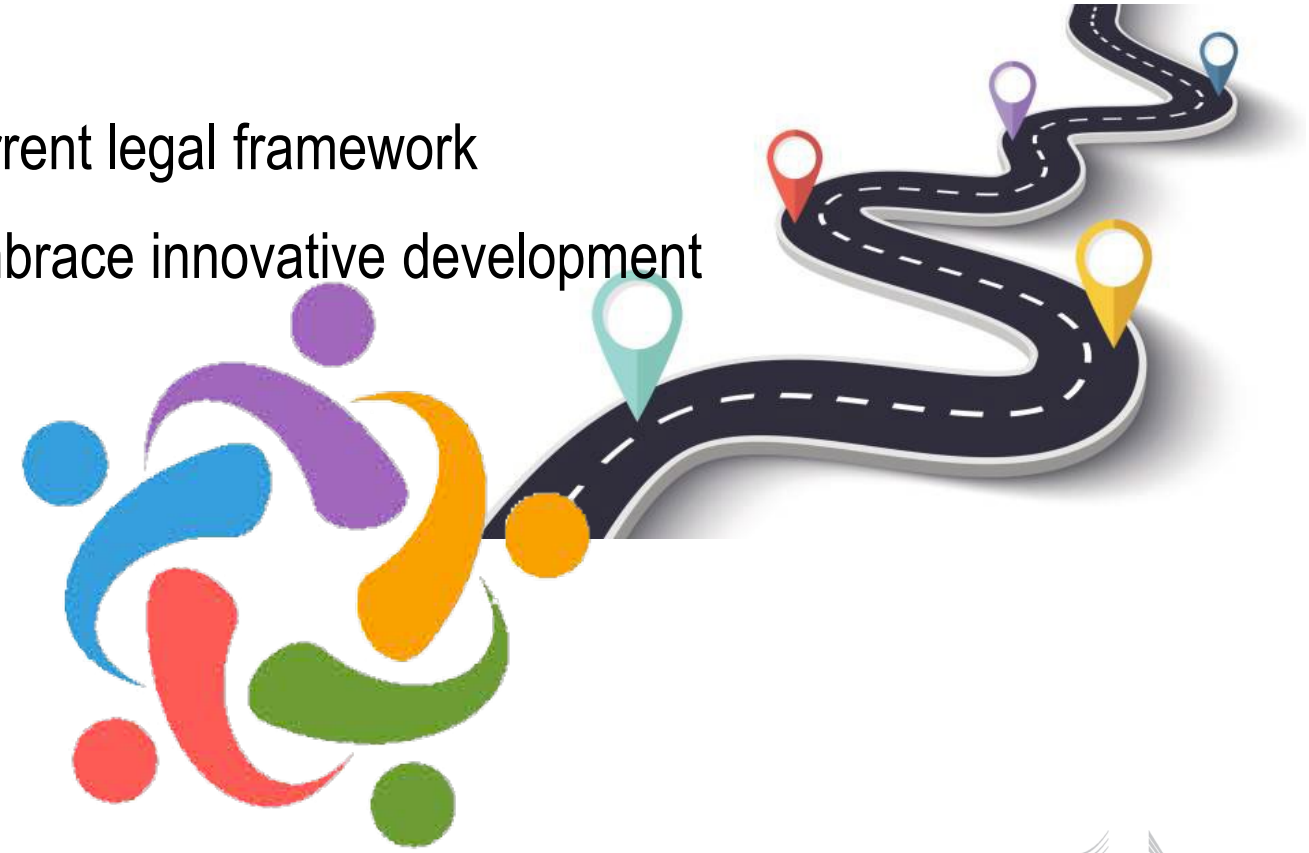
In light of the EP Resolution of Sept 2021, the European Citizens Initiative as well as discussions in context of the targeted revision of REACH, Commission and ECHA agreed to work towards a Roadmap for conducting chemical safety assessment without animal testing.

The roadmap is looking to

- Identifying critical needs necessary to transit to animal free system to steer NAM methodological developments
- Apply what is already available under the current system
- Re-think the overall system to accommodate NAMs, Re-define the main elements of the horizontal approach

Enhanced collaboration between key-players

- Set goals together with research projects (PARC) to reach regulatory acceptable NAM solutions
- Consider experience gained in the current legal framework
- Ensure current protection level but embrace innovative development
- Create confidence together
- Agree a common roadmap



BRIDGE BUILDERS

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REACH - Indicative timing of actions

- Supporting actions and studies – **Q1 2021 to Q4 2022**
- Impact Assessment – **Autumn 2021 to Autumn 2022**
- Drafting proposal for revision of REACH – **2022/2023**
- Commission adoption of proposal – **Q4 2023 at the latest**

Delegated act for new hazard classes

- Draft published for consultation on “Have your say” 20 September – 18 October 2022
  https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/13578-Introducing-new-hazard-classes-CLP-revision_en

- Adoption: 19th December 2022 after CARACAL discussion and WTO TBT notification
- Publication: Q1 2023 after scrutiny period (EU Parliament + Council)
- Transitional period: 24 months for substances and 36 months for mixtures

New hazard classes Endocrine Disruptors for human health and environment

- Persistent Bioaccumulative and Toxic (PBT) and very Persistent and very Bioaccumulative (vPvB)
- Persistent Mobile and Toxic (PMT) and very Persistent and very Mobile (vPvM)

Thank you

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